Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 71-73, 75-78, 80-82 and 99 are pending in the application, with claims 71 and 80 being the independent claims. Claim 80 was amended taking the Examiner's comments into consideration. In particular, the claim was amended to indicate that the purified or isolated ICAM-1 binds with specificity to the ICAM-1 monoclonal antibody RR1/1. Support for this language can be found in priority application 07/045,963, at pages 38-43 (Examples 8 and 9). Thus, no new matter has been added by this amendment.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Objections to the Drawings

The Examiner indicated that formal drawings and photographs were submitted that fail to comply with 37 C.F.R. § 1.84. (Paper No. 28, at page 2.) Applicants respectfully indicate that formal drawings or photographs have not yet been submitted. However, Applicants will submit formal drawings upon an indication of allowable subject matter by the Examiner.

Rejections under 35 U.S.C. § 112

The Examiner rejected claims 80-82 under35 U.S.C. §112, first paragraph, because

allegedly the specification does not enable any person skilled in the art to which it pertains, or with which it is most clearly connected, to make and use the invention commensurate in scope with the claims. (Paper No. 28, at page 3.) According to the Examiner, "the specification, while being enabling for 'purified or isolated ICAM-1' which is bound by the RR-1 or defined by the amino acids of Figure 8, does not reasonably provide enablement for any 'purified or isolated ICAM-1'." *Id.*

As the Examiner acknowledged, the specification is enabling for a purified or isolated ICAM-1 which is bound by the RR1/1 ICAM-1 antibody. Thus, Applicants have amended claims 80-82 to indicate that the purified or isolated ICAM-1 is bound by the RR1/1 ICAM-1 antibody. Since the RR1/1 ICAM-1 antibody is readily available to the public (*see* discussion below regarding the deposit requirement), withdrawal of this rejection is respectfully requested.

The Examiner rejected claims 71-73, 75-78, 80-82 and 99 stating that

> [i]t is apparent that the RR1/1 antibody is required to practice the claimed invention. As a required element, it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If it is not so obtainable or available, the enablement requirements of 35 USC 112, first paragraph, may be satisfied by a deposit of the cell line/hybridoma which produces this antibody.

Paper No. 28, at page 3.

Applicants submit that the RR1/1 antibody is both widely known and readily obtainable. In addition, no deposit is required where the required biological materials can be obtained from publicly available material with only routine experimentation and a reliable screening test. *See* M.P.E.P. § 2404.02 at 2400-6. Applicants submit that the RR1/1 antibody can be made or isolated by one skilled in the art without undue experimentation as taught in the specification. For example, the specification, at pages 50-

51, sets forth a detailed description of the preparation and screening of the RR1/1 antibody. Since the RR1/1 antibody can be obtained from publicly available material with only routine experimentation and a reliable screening test, no deposit is required.

In addition, the RR1/1 antibody is commercially available from Bender-Medsystems (MedSystems Diagnostics GmbH, Rennweg 95b,1030 Vienna, Austria, phone: 011-43-1-796 40 40-0) (*see also* Attachment A). Applicants point out that the Patent and Trademark Office has indicated that it will accept commercial availability as evidence that a biological material is known and readily available when the evidence is clear and convincing that the public has access to the material. *See* M.P.E.P. § 2404.01 at 2400-5. Since the RR1/1 antibody is readily accessible to the public from Bender-Medsystems, a deposit is not required. Thus, withdrawal of this rejection is respectfully requested.

The Examiner further rejected claims 75-78 and 80-82 under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. (Paper No. 28, at page 4.) According to the Examiner,

> claims 80-82 are indefinite in that they only describe the compositions of interest by an arbitrary protein name. While the name itself may have some notion of the activity of the protein, there is nothing in the claims which distinctly claims the protein and variants thereof. For example, others in the field may isolate the same protein and give such an entirely different name. Applicant should particularly point out and distinctly claim "ICAM-1" by claiming characteristics associated with the protein (e.g. amino acid composition, specifically bound by a deposited antibody,; e.g. RR/1).

Id.

Applicants respectfully disagree. However, in an effort to advance prosecution, Applicants have amended claims 80-82 to indicate that the purified or isolated ICAM-1

binds with specificity to the ICAM-1 monoclonal antibody RR1/1. Support for this language can be found in priority Appl. No. 07/045,963, at pages 38-43 (Examples 8 and 9). Thus, this rejection is moot.

With respect to claims 75-78, the Examiner stated that

> in consideration of the discrepancies often encountered in the art between protein molecular weight when determined by different methods, when a molecular weight is recited to characterize a protein the claims should include not only the method by which it was determined, e.g. whether by sodium dodecyl sulphate polyacrylamide gel electrophoresis, gel filtration or some other method, but also whether the determination was made under denaturing or non-denaturing conditions and whether reducing or non-reducing conditions were are [sic] used.

Id.

Applicants respectfully traverse this rejection. The test for indefiniteness is whether the scope of the claim is clear to a hypothetical person possessing an ordinary level of skill in the pertinent art. *See* M.P.E.P. § 2173.02 at 2100-145 (2000). Claims 75-78 recite the molecular weight of ICAM-1 as determined by sodium dodecyl sulphate (SDS) polyacrylamide gel electrophoresis. Applicants submit that SDS polyacrylamide gel electrophoresis, by definition, is done under denaturing conditions since SDS is a denaturing agent. Furthermore, the specification discloses that under either reducing or non-reducing conditions ICAM-1 runs on a SDS polyacrylamide gel with the same apparent molecular weight (*see* specification at page 52 and Figures 5A and 5B). Thus, it is not necessary to indicate whether reducing or non-reducing conditions were used, as the molecular weight of ICAM-1 remains the same. Clearly, the scope of the claim will be clear to one skilled in the art. Therefore, withdrawal of this rejection is respectfully requested.

Rejections under 35 U.S.C. § 102

The Examiner rejected claims 71-73, 75-78, 80-82 and 99 under 35 U.S.C. §102(b) as allegedly being anticipated by Tomassini (Ph.D. Dissertation, 1986) ["Tomassini thesis"], Tomassini *et al.* (*J. Virol. 58*:290-295 (1986)) ["Tomassini article"], and Colonno *et al.* (Virus Attachment and Entry into Cells, Proceedings of an ASM Conference held in Philadelphia, PA, April 10-13, 1985) ["Colonno"]. (Paper No. 28, at page 5.) The Examiner stated that "no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced rhinovirus receptor." *Id.*

The Examiner is reminded that for a 102(b) rejection to be proper, each and every element of the claims must be found in the cited references. Also, the identical invention must be shown in as complete detail as is contained in the . . . claim. M.P.E.P. § 2131 at 2100-54 (2000). Furthermore, to anticipate, the reference must also enable one of skill in the art to make and use the claimed invention. *In re Donohue*, 766 F.2d 531, 533, 226 U.S.P.Q. 619, 621 (Fed. Cir. 1985).

The isolation and purification of an active form of a membrane-associated protein, such as ICAM-1, is highly dependent on the purification procedure used. Integral membrane proteins require high concentrations of detergent for solubilization, generally complete solubilization is needed to release them. These proteins are normally neither soluble nor stable in the absence of detergent. *Current Protocols in Protein Science*, Strategies for Protein Purification, Unit 1.2 at 1.2.2 (1995). It is sometimes necessary to maintain natural phospholipids in association with the proteins in order to maintain activity. Furthermore, purification processes may be affected by the presence of detergents. *Id.*

Applicants submit that the Tomassini thesis and article do not anticipate the claimed invention because they do not enable one skilled in the art to make and use the claimed invention. In fact, the authors of the Tomassini thesis and article indicate that using their purification procedure, they are unable to isolate a 90-kDa receptor protein (ICAM-1) capable of binding virus (Tomassini thesis at 116, line 22, to 117, line 1; and Tomassini article at 295, col. 1, lines 20-25.) Thus, the purification procedures taught in the Tomassini thesis and Tomassini article appear to disrupt the ICAM-1 receptor structure such that HRV binding activity is eliminated. Since the binding sites for HRV and LFA-1 overlap, one of ordinary skill in the art would expect that any disruption in structure from the purification procedure leading to the elimination of HRV binding, would also reduce or eliminate LFA-1 binding. Thus, the Tomassini thesis and the Tomassini article teach the isolation and characterization of an inactive form of ICAM-1, which is incapable of binding to HRV, LFA1, Mac-1 or p150,95.

Moreover, Colonno *et al.* show "a predominant protein band migrating with an apparent molecular weight of 90,000 (J. E. Tomassini and R. J. Colonno, submitted for publication)." (Colonno *et al.*, page 113, lines 29-31.) However, "[f]urther analysis of this candidate receptor protein is in progress." *Id.* at lines 34-35. Thus, Colonno *et al.*, mentions the Tomassini article discussed above for further analysis of the receptor protein. As discussed above, neither the Tomassini article nor the Tomassini thesis teach the isolation of an active form of ICAM-1, capable of binding to HRV, LFA-1, Mac-1 or p150,95.

In contrast, Applicants' purification procedure taught in the specification enables isolation of a functional HRRP receptor (ICAM-1), capable of binding to LFA-1, Mac-1 or p150,95. Since it is generally known in the art that activity of an isolated and purified protein depends primarily on the purification procedure used, the claimed functional

limitations cannot be inherent properties of the referenced rhinovirus receptor. Moreover, the art cited by the Examiner is proof that protein purification procedures may or may not result in the isolation of a functional protein. Since the Tomassini thesis and the Tomassini article do not teach the isolation of ICAM-1 in active form as presently claimed, this rejection should be withdrawn.

The Examiner stated that "[t]he burden is on the applicant to establish a patentable distinction between the claimed and referenced products." (Paper No. 28, at page 6.) Applicants submit that they have met this burden. As discussed above, the art cited by the Examiner does not teach the isolation and purification of ICAM-1 in active form as presently claimed.

Rejections under 35 U.S.C. § 103

Claims 71-73, 75-78, 80-82 and 99 were rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Tomassini (Ph.D. Dissertation, 1986) and/or Tomassini *et al.* (*J. Virol. 58*:290-295 (1986)) and/or Colonno *et al.* (Virus Attachment and Entry into Cells, Proceedings of an ASM Conference held in Philadelphia, PA, April 10-13, 1985). (Paper No. 28, at page 6.)

Regarding claims 71-73, 75-78 and 99, the Examiner stated that

> [i]t is noted the prior art teaches the isolation and characterization of the rhinovirus receptor which reads on the claimed ICAM-1 preparations. Given applicant's arguments that the prior art isolated prior art rhinovirus receptor may not have the properties of binding LFA-1/Mac-1/p150,95; it is noted that prior art rhinovirus receptor is clearly identified as being the receptor for rhinovirus receptor. Given this clear teaching and the clear motivation of the ordinary artisan to characterize this protein further, as taught by the each reference; the ordinary artisan would have been able to

> isolate and characterize the HRV receptor with the known and desired functional properties, such as HRV binding.

Paper No. 28, at page 6.

Here, as discussed above, Applicants point out that the isolated and purified rhinovirus receptor of the prior art is nonfunctional and not capable of binding to HRV. (*See* Tomassini thesis at 116, line 22, to 117, line 1; and Tomassini article at 295, col. 1, lines 20-25.) Thus, one skilled in the art following the purification procedure outlined by Tomassini, would end up with a nonfunctional ICAM-1 preparation. The Examiner has not cited any art which teaches a purification procedure of ICAM-1 in which the ICAM-1 preparation retains the ability to bind HRV. From the teachings of the references, one skilled in the art would have no reasonable expectation of success in producing an ICAM-1 preparation capable of binding to HRV, LFA-1, Mac-1 or p150,95.

The Examiner further stated that "the thesis clearly states that the HRV receptor is utilized by the major groups of HRVs during attachment to cells (page 65, and Discussion on pages 107-118). Additional biochemical studies (pages 69-83) as well as initial cloning of the HRV receptor (pages 83-105) are also disclosed." (Paper No. 28, at page 7.)

Applicants submit that the thesis does not teach the isolation and purification of an active form of ICAM-1 capable of binding to HRV, LFA-1, Mac-1 or p150,95. The pages of the thesis the Examiner is referring to show, for example, that addition of increasing amounts of receptor antiserum corresponded to an increased inhibition of ^{35}S-labeled HRV binding to HeLa membranes. No inhibition of virus binding was observed with dilutions of control antiserum. (Tomassini thesis at page 65, lines 4-8.) The thesis further shows that ICAM-1 is a glycoprotein (*see* pages 69-83). Moreover, the Discussion section of the thesis states that "it is quite tempting to speculate that a pentamer of the 90-kDa receptor protein

is needed for a functional receptor complex. This would correlate well with the 440-kDa receptor peak obtained by gel filtration and the inability to isolate a 90-kDa receptor protein capable of binding virus." (Tomassini thesis at page 116, line 22, to page 117, line 1.) Thus, the pages of the thesis recited by the Examiner do not teach the isolation and purification of an active form of ICAM-1 capable of binding to HRV, LFA-1, Mac-1 or p150,95.

Furthermore, Dr. Rothlein, in his Rule 132 Declaration submitted on October 24, 2000, discussed the fact that the cDNA clones disclosed in the Tomassini thesis would not express ICAM-1, and that the clones represent a cloning artifact or a fortuitous cross-reactivity of the anti-HRV-receptor antibody with another anti-ICAM-1 protein.

As further evidence that the Tomassini clones do not comprise the actual ICAM-1 gene, a subsequent article published by the author of the thesis, Tomassini *et al.*, *Proc. Natl. Acad. Sci. 86*:4907-4911 (1989) (not prior art), teaches the cloning of the ICAM-1 gene. (*See* Exhibit H submitted with the Rule 132 Declaration.) To obtain the cloned gene, Tomassini *et al.* used a different cDNA library and different clones than the library and clones described in the thesis. If the clones described in the thesis actually contained the ICAM-1 gene, it would not have been necessary to clone the ICAM-1 gene from another source. Finally, the monoclonal antibody directed against the HRV receptor (ICAM-1) did not recognize the protein expressed from clone 4A, showing that the portion of ICAM-1 recognized by the antibody was not expressed in its native state. (Tomassini thesis at 85, lines 16-20.)

In summary, the passages of the thesis recited by the Examiner do not teach the isolation and purification of an active form of ICAM-1 capable of binding to HRV, LFA-1, Mac-1 or p150,95.

Regarding claims 80-82, the Examiner alleged that

> these references do not teach the use of artificial lipid membranes per se. However, providing proteins of interest in artificial lipid membranes in a variety of means for a variety of purposes for the characterization and determination of the structure-function of a protein of interest was well known and practiced at the time the invention was made.

Paper No. 28, at page 6.

Applicants contend that one with ordinary skill in the art would not have had reason to expect that their HRRP (ICAM-1) purification procedure would yield HRRP capable of binding to LFA-1, Mac-1, or p150,95. In fact, the authors of the Tomassini thesis and the Tomassini article indicate that they are unable to isolate a 90-kDa receptor protein capable of binding virus. Thus, the purification procedure taught by Tomassini renders the isolated HRRP preparation nonfunctional. Based on the teachings of the Tomassini thesis and the Tomassini article, and the fact that the binding sites for LFA-1 and HRV overlap, one of ordinary skill in the art would have no reason to believe that purified HRRP would bind to LFA-1, Mac-1, or p150,95. Therefore, the Tomassini thesis and the Tomassini article do not teach the isolation of HRRP in active form. No other art has been cited by the Examiner to establish the purification of HRRP in an active form.

In contrast, Applicants' purification procedure as taught in the specification enables isolation of a functional HRRP receptor, capable of binding to LFA-1, Mac-1 or p150,95. Since the Tomassini thesis and the Tomassini article do not teach the isolation of HRRP in active form as presently claimed, this rejection should be withdrawn.

The Examiner further stated that "[e]ven if there is an indication that there may be reduced binding of a particular radiolabeled HRV receptor preparation reduced binding to HRV [sic]; it maintained the ability to bind." (Paper No. 28, at page 8.)

Applicants respectfully disagree. There was no indication of reduced binding of the radiolabeled HRV receptor preparation to HRV; there was *no* binding.

The Examiner also recited *Atlas Powder Co. v. IRECO*, 51 USPQ2d 1943 (Fed. Cir. 1999). (Paper No. 28, at page 8.) Applicants submit that the Examiner's quote is incomplete and out of context. The passage the Examiner should have quoted states that

> in *Titanium Metals*, the patent applicants sought a patent for a titanium alloy containing various ranges of nickel, molybdenum, iron, and titanium. The claims also required that the alloy be "characterized by good corrosion resistance, in hot brine environments." *Titanium Metals*, 778 F.2d at 776. A prior art reference disclosed a titanium alloy falling within the claimed ranges, but did not disclose any corrosion-resistant properties. This court affirmed a decision of the PTO Board of Appeals finding the claimed invention unpatentable as anticipated. This court concluded that the claimed alloy was not novel, noting that "it is immaterial, on the issue of their novelty, what inherent properties the alloys have or whether these applicants discovered certain inherent properties." *Id.* at 782. This same reasoning holds true when it is not a property, but an ingredient, which is inherently contained in the prior art.

Atlas Powder Co. v. IRECO, 51 U.S.P.Q.2d 1943, 1947 (Fed. Cir. 1999). Applicants submit that in contrast to the facts set forth in *Titanium Metals*, the Tomassini thesis and article do not show that the ICAM-1 preparation is functional but fail to disclose binding to HRV; instead, the Tomassini thesis and article state that their ICAM-1 preparation is incapable of binding to HRV. Thus, Applicants submit that *Atlas Powder Co. v. IRECO* does not apply here.

Applicants submit that the other cases cited by the Examiner, namely, *In re Best*, 195 USPQ 430 (CCPA 1977), *In re Marosi*, 218 USPQ 289 (Fed. Cir. 1983), *In re Fitzgerald*, 205 USPQ 594 (CCPA 1980), *Ex parte Raske*, 28 USPQ2d 1304 (BPAI 1993) and *In re Spada*, 15 USPQ2d 1655 (Fed. Cir. 1990) all relate to small organic molecules or chemicals

and other compounds (zeolitic molecular sieve catalyst compositions, zeolitic compounds, self-locking screw-threaded fasteners, branched polyethylene pipe, and pressure sensitive adhesive composition, respectively). These cases do not recite biological molecules such as proteins.

In contrast, Applicants' claimed invention relates to an isolated and purified ICAM-1 preparation, capable of binding to LFA-1, Mac-1 or p150,95. As discussed above, isolating and purifying an active form of a membrane-associated protein like ICAM-1 is highly dependent on the purification procedure used. *See Current Protocols in Protein Science*, Strategies for Protein Purification, Unit 1.2 at 1.2.2 (1995). There is no guarantee that an isolated and purified protein will retain activity. This is clearly shown by the authors of the Tomassini thesis and article who indicate that they are unable to obtain an active form of ICAM-1 capable of binding HRV. Since the Tomassini thesis and the Tomassini article do not teach the isolation of HRRP in active form as presently claimed, withdrawal of this rejection is respectfully requested.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite

prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Gaby Longsworth

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Agent for Applicants
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SKGF Rev. 2/13/01

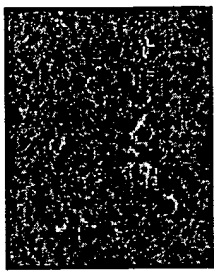
Version with markings to show changes made

80. (Thrice Amended) An artificial lipid membrane comprising purified or isolated ICAM-1, wherein said purified or isolated ICAM-1 is derived from human cells or tissues, is substantially free of natural protein contaminants in said artificial lipid membrane, and is capable of binding to LFA-1, Mac-1, or p150,95; and

wherein said purified or isolated ICAM-1 binds with specificity to the ICAM-1 monoclonal antibody RR1/1.

Bender MedSystems Products

human anti-ICAM-1 FITC



Cat.No.: BMS108FI

Form: FITC

Volume: 1 ml

Quantity: 100 Tests*

Clone: RR1/1

Subclass: mouse IgG1

Purity: > 95% IgG1 as determined by SDS-gel electrophoresis prior to addition of stabilizer and preservative.

Presentation: 50 mM TRIS/100 mM NaCl/1% BSA/0.02% Sodium Azide, pH7.4

Specificity: BMS108 specifically reacts with human ICAM-1.

Cross-reactivity: BMS108 does not cross-react with mouse or with rhesus

Applications:

Immunohistochemistry:

The antibody can be used to stain aceton-fixed cryostat sections or cell smears. Recommended for BMS108 is the alkaline phosphatase-anti-alkaline-phosphatase (APAAP), or peroxidase anti-peroxidase (PAP) procedures or the three stage immunoperoxidase technique on aceton-fixed cryostat sections. BMS108 may be used at a concentration of 1,25-0,5μg/ml. Optimal dilutions should be determined by the individual laboratory for each application.

Paraffin sections:

BMS108 has not been successfully used in paraffin-embedded tissue.

Flow cytometry:

BMS108 is also suitable as primary antibody in staining for FACS analysis, BMS108FI can be used for direct staining of cells, BMS108BT can be used in a two-step procedure using the biotin-(strept-)avidin system. Recommended dilution is 1:20 as determined on RPMI8866 cells (for exact concentration see vial label). See protocol below.

Functional studies:

RR1/1 can be used as a neutralizing agent. See protocol below

Optimal dilutions should be determined by the individual laboratory for each application.

Western blot:

BMS108 is suitable for Western blot analysis. See protocol below.

Storage: 2-8°C

Shipping Conditions: 2-8°C

General
References